Dynamic distribution of linker histone H1.5 in cellular differentiation.

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Public Summary:
In this paper we showed that a structural protein named H1.5 binds to specific places across the human genome in cells that have fully differentiated to distinctive cell types but not in embryonic stem cells or progenitor cells. This protein which is mutated in certain colon cancers causes compaction of the regions to which it binds, causing lasting repression of gene expression. Our data suggest that this protein stabilizes the identity of cells once they have differentiated and functionally specialized. This would be why H1.5 is not bound to the genome in embryonic stem cells because these cells need to retain their potential to differentiate to other cell types. Since differentiated cells divide only for a limited number of times, mutation of H1.5 in colon cancer may allow the cancer cells to reverse their differentiated state so that they can divide indefinitely.

Scientific Abstract:
Linker histones are essential components of chromatin, but the distributions and functions of many during cellular differentiation are not well understood. Here, we show that H1.5 binds to genic and intergenic regions, forming blocks of enrichment, in differentiated human cells from all three embryonic germ layers but not in embryonic stem cells. In differentiated cells, H1.5, but not H1.3, binds preferentially to genes that encode membrane and membrane-related proteins. Strikingly, 37% of H1.5 target genes belong to gene family clusters, groups of homologous genes that are located in proximity to each other on chromosomes. H1.5 binding is associated with gene repression and is required for SIRT1 binding, H3K9me2 enrichment, and chromatin compaction. Depletion of H1.5 results in loss of SIRT1 and H3K9me2, increased chromatin accessibility, deregulation of gene expression, and decreased cell growth. Our data reveal for the first time a specific and novel function for linker histone subtype H1.5 in maintenance of condensed chromatin at defined gene families in differentiated human cells.